FORMULATION FOR ORAL DELIVERY OF PROTEINS, PEPTIDES AND SMALL MOLECULES WITH POOR PERMEABILITY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the priority of U.S. Provisional Application No. 62/832,508, filed April 11, 2019, the entire contents of which are incorporated herein by reference.

FIELD OF THE DISCLOSURE

[0002] This disclosure relates to a formulation for oral delivery of proteins, peptides and small molecules with poor permeability. More specifically, this disclosure relates to a pharmaceutical formulation intended for oral delivery of any molecule synthetic or natural with poor permeability or salts or solvates thereof having a therapeutic activity.

BACKGROUND OF THE INVENTION

[0003] Poorly permeable molecules are compounds that have poor absorption through the intestinal membrane. As such, they are administered intravenously or subcutaneously. Because of their poor absorption through the intestinal membrane, their clinical use is considerably restricted given the need to be administered IV and dosed several times a day (e.g., insulin for diabetics). These poorly permeable compounds are identified as BCS class III and class IV compounds in the classification proposed by Amidon GL et al in *A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability* (Pharm Res. 1995 Mar;12(3):413-20.), which is hereby incorporated by reference in its entirety.

SUMMARY

[0003a] In an aspect of the present disclosure, there is provided a pharmaceutical formulation, comprising:

a synthetic or natural poorly permeable calcitonin gene-related peptide (CGRP) inhibitor or salt or solvate thereof comprising (R)-N-(3-(7-methyl-1H-indazol-5-yl)-1-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidine-1-carboxamide (BHV-3500) in an amount 0.01-20 wt.% of the total weight of the formulation;

a lipophilic phase comprising triglycerides of fatty acids comprising medium chain fatty acids in an amount of 50-80 wt.% of the total weight of the formulation; and

at least one lipophilic surfactant comprising partial esters of polyol and fatty acids comprising a mixture of mono and diglyceride of medium chain fatty acids in an amount of 10-50 wt.% of the total weight of the formulation, wherein the formulation does not include water.

[0003b] In another aspect of the present disclosure, there is provided a delayed release pharmaceutical dosage form comprising:

a pharmaceutical formulation comprising:

a synthetic or natural poorly permeable CGRP inhibitor or salt or solvate thereof comprising (R)-N-(3-(7-methyl-1H-indazol-5-yl)-1-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidine-1-carboxamide (BHV-3500) in an amount 0.01-20 wt.% of the total weight of the formulation;

a lipophilic phase comprising triglycerides of fatty acids comprising medium chain fatty acids in an amount of 50-80 wt.% of the total weight of the formulation; and

at least one lipophilic surfactant comprising partial esters of polyol and fatty acids comprising a mixture of mono and diglyceride of medium chain fatty acids in an amount of 10-50 wt.% of the total weight of the formulation, wherein the delayed release dosage form is a coated dosage form whose release is pH dependent and the formulation does not include water.

[0003c] In a further aspect of the present disclosure, there is provided a pharmaceutical formulation for use in treating a patient, wherein an effective amount of the pharmaceutical formulation is to be administered to the patient, and wherein the pharmaceutical formulation comprises:

a synthetic or natural poorly permeable CGRP inhibitor or salt or solvate thereof comprising (R)-N-(3-(7-methyl-1H-indazol-5-yl)-1-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidine-1-carboxamide (BHV-3500) in an amount 0.01-20 wt.% of the total weight of the formulation;

a lipophilic phase comprising triglycerides of fatty acids comprising medium chain fatty acids in an amount of 50-80 wt.% of the total weight of the formulation; and

at least one lipophilic surfactant comprising partial esters of polyol and fatty acids comprising a mixture of mono and diglyceride of medium chain fatty acids in an amount of 10-50 wt.% of the total weight of the formulation, wherein the formulation does not include water.

[0004] Applicants have developed formulations for orally administered molecules with poor permeability. The molecule may be a CGRP inhibitor. These formulations are highly beneficial for patients that require dosing several times a day. In order to prepare such formulations for oral delivery of poorly permeable CGRP inhibitors, Applicants had to overcome at least this poor permeability against the intestinal membrane; and for some of those inhibitors in particular peptides and proteins the chemical and physical instability in the gastrointestinal tract and specifically, the loss of activity due to acidic conditions in the

CLAIMS

1. A pharmaceutical formulation, comprising:

a synthetic or natural poorly permeable calcitonin gene-related peptide (CGRP) inhibitor or salt or solvate thereof comprising (R)-N-(3-(7-methyl-1H-indazol-5-yl)-1-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidine-1-carboxamide (BHV-3500) in an amount 0.01-20 wt.% of the total weight of the formulation;

a lipophilic phase comprising triglycerides of fatty acids comprising medium chain fatty acids in an amount of 50-80 wt.% of the total weight of the formulation; and

at least one lipophilic surfactant comprising partial esters of polyol and fatty acids comprising a mixture of mono and diglyceride of medium chain fatty acids in an amount of 10-50 wt.% of the total weight of the formulation, wherein the formulation does not include water.

~~2. The formulation of claim 1, wherein the synthetic or natural poorly permeable CGRP inhibitor is a CGRP antibody, a CGRP receptor antibody, an antigen-binding fragment from a CGRP antibody or a CGRP receptor antibody, a CGRP infusion inhibitory protein, a CGRP bio-neutralizing agent, a small molecule CGRP receptor antagonist, a small molecule CGRP inhibitor, or a polypeptide CGRP inhibitor.~~

~~3. The formulation of claim 1, wherein the synthetic or natural poorly permeable CGRP inhibitor is a small molecule CGRP receptor antagonist.~~

~~4. The formulation of claim 3, wherein the small molecule CGRP receptor antagonist is (R)-N-(3-(7-methyl-1H-indazol-5-yl)-1-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidine-1-carboxamide (BHV-3500).~~

~~5.~~2.The formulation of claim 1, further comprising at least one hydrophilic surfactant with a hydrophilic lipophilic balance (“HLB”) above 10 in an amount of 1-30 wt.% of the total weight of the formulation.

~~6.~~3.The formulation of claim ~~5~~2, wherein the at least one hydrophilic surfactant is selected from the group consisting of polyoxyethylene (20) monooleate, PEG 8

caprylic/capric glycerides, PEG 6 caprylic/capric glycerides, poly(oxyethylene)(4)Lauryl ether and mixtures thereof.

~~7. The formulation of claim 1, wherein the triglycerides of fatty acids are medium chain fatty acids.~~

~~8. The formulation of claim 1, wherein the lipophilic surfactant comprises a mixture of mono and diglyceride of medium chain fatty acids.~~

~~9. The formulation of claim 1, wherein the formulation does not include water.~~

~~10.~~4. A delayed release pharmaceutical dosage form comprising:

a pharmaceutical formulation comprising:

a synthetic or natural poorly permeable CGRP inhibitor or salt or solvate thereof comprising (R)-N-(3-(7-methyl-1H-indazol-5-yl)-1-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidine-1-carboxamide (BHV-3500) in an amount 0.01-20 wt.% of the total weight of the formulation;

a lipophilic phase comprising triglycerides of fatty acids comprising medium chain fatty acids in an amount of 50-80 wt.% of the total weight of the formulation; and

at least one lipophilic surfactant comprising partial esters of polyol and fatty acids comprising a mixture of mono and diglyceride of medium chain fatty acids in an amount of 10-50 wt.% of the total weight of the formulation, wherein the delayed release dosage form is a coated dosage form whose release is pH dependent and the formulation does not include water.

~~11.~~5. A pharmaceutical formulation for use in treating a patient, wherein an effective amount of the pharmaceutical formulation is to be administered to the patient, and wherein the pharmaceutical formulation comprises:

a synthetic or natural poorly permeable CGRP inhibitor or salt or solvate thereof comprising (R)-N-(3-(7-methyl-1H-indazol-5-yl)-1-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidine-1-carboxamide (BHV-3500) in an amount 0.01-20 wt.% of the total weight of the formulation;

a lipophilic phase comprising triglycerides of fatty acids comprising medium chain fatty acids in an amount of 50-80 wt.% of the total weight of the formulation; and

at least one lipophilic surfactant comprising partial esters of polyol and fatty acids comprising a mixture of mono and diglyceride of medium chain fatty acids in an amount of 10-50 wt.% of the total weight of the formulation, wherein the formulation does not include water.

~~12. The pharmaceutical formulation for use of claim 11, wherein the synthetic or natural poorly permeable CGRP inhibitor is a CGRP antibody, a CGRP receptor antibody, an antigen-binding fragment from a CGRP antibody or a CGRP receptor antibody, a CGRP infusion inhibitory protein, a CGRP bio-neutralizing agent, a small molecule CGRP receptor antagonist, a small molecule CGRP inhibitor, or a polypeptide CGRP inhibitor.~~

~~13. The pharmaceutical formulation for use of claim 11, wherein the synthetic or natural poorly permeable CGRP inhibitor is a small molecule CGRP receptor antagonist.~~

~~14. The pharmaceutical formulation for use of claim 13, wherein the small molecule CGRP receptor antagonist is (R)-N-(3-(7-methyl-1H-indazol-5-yl)-1-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidine-1-carboxamide (BHV-3500).~~

~~15.~~6. The pharmaceutical formulation for use of claim ~~11~~5, wherein the pharmaceutical formulation comprises at least one hydrophilic surfactant with a hydrophilic lipophilic balance ("HLB") above 10 in an amount of 1-30 wt.% of the total weight of the formulation.

~~16.~~7. The pharmaceutical formulation for use of claim ~~15~~6, wherein the at least one hydrophilic surfactant is selected from the group consisting of polyoxyethylene (20) monooleate, PEG 8 caprylic/capric glycerides, PEG 6 caprylic/capric glycerides, poly(oxyethylene)(4)Lauryl ether and mixtures thereof.

~~17. The pharmaceutical formulation for use of claim 11, wherein the triglycerides of fatty acids are medium chain fatty acids.~~

~~18. The pharmaceutical formulation for use of claim 11, wherein the lipophilic surfactant comprises a mixture of mono and diglyceride of medium chain fatty acids.~~

~~19. The pharmaceutical formulation for use of claim 11, wherein the formulation does not include water.~~

~~20.~~8. The pharmaceutical formulation for use of claim ~~11~~5, wherein the pharmaceutical formulation is in a delayed release dosage form comprising a coated dosage form whose release is pH dependent.